Editorial

Time interval of neoadjuvant chemotherapy to surgery in breast cancer: how long is acceptable?

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Time interval to treatment is an important question asked by patients every day, but also a question without a definite answer. Clinical practice guidelines do not present specific guidelines on a maximum interval and conflicting results are reported in numerous studies (1-4). This question has also been discussed in various intervals, as of time interval between diagnosis to surgery, and surgery to adjuvant chemotherapy or radiotherapy. An article by Sanford *et al*. (5) in a recent issue of *Ann Surg Oncol*, has approached this topic in a different aspect, as a time interval between completion of neoadjuvant treatment and surgery. As the authors have pointed out, this is the first article to evaluate this specific time interval.

Sanford *et al*. (5) analyzed data from a single institution, The University of Texas MD Anderson Cancer Center, of 1,101 patients who were treated with neoadjuvant chemotherapy. Time interval between completion of neoadjuvant chemotherapy and surgery was divided into three groups: ≤4, >4–6 and >6–24 weeks. Patients in all three groups had no difference in overall survival, recurrence-free survival and locoregional recurrence-free survival. However, sensitivity analysis comparing ≤8 weeks to a small group of 8–24 weeks (6.4%) presented worse outcomes when surgery was performed after over 8 weeks.

Current evidence shows that treatment delays are lengthening over time (6,7), and the need for investigation of the impact of these delays in various intervals is an increasingly important consideration. Sanford *et al*. (5) also presented a considerable number of patients, more than one-fifth of all patients, having a time interval of more than 6 weeks between completion of neoadjuvant chemotherapy and surgery. The period or reasons for this delay were not mentioned, but these delays are not unexpected considering the increased need for multidisciplinary approaches including, genetic testing and reconstructive counseling.

This issue of time interval between completion of neoadjuvant chemotherapy and surgery has also not been well addressed in large randomized clinical trials on neoadjuvant systemic therapy and many do not even specify the recommended interval (8-10). But when mentioned, a surgery between 2 and 5 weeks after the last chemotherapy cycle was recommended (11-13). In the clinic, accepted practice is to perform surgery when the neutropenic window is overcome, normally resulting in a 3- to 4-week interval. However, the acceptable maximum interval is unknown and with the start of this study by Sanford *et al*. (5), further investigation will be needed.

A result that should also be paid attention to in this article (5), is the significantly lower pathologic complete response (pCR) rate in patients who underwent surgery of more than 6 weeks later (0–4 weeks, 17.0%; 4–6 weeks, 20.4%; >6 weeks, 12.8%; P value 0.03). This difference

did not lead to worse patient survival and the impact of numerous factors that could confound analysis of the correlation is unknown as additional multivariate analysis was not performed. However, a lower proportion of pCR in patients with an interval of more than 6 weeks, does give the possibility of a hypothesis of tumor cell rebound growth after a long period of chemotherapy wash out. Recently in a neoadjuvant phase II trial, a rebound increase of Ki-67 level after a wash-out period of 4 weeks of palbociclib was presented which was not shown in patients receiving additional palbociclib immediately before surgery, implying the potential of this theory (14). Even putting aside the possibility of this theory, a delay of more than 6 weeks to surgery can be quite hesitative, considering the lower rate of pCR in the delayed group and the survival benefit of pCR on individual level (15).

Like previous studies in this area, the study by Sanford *et al*. (5) has the inherent pitfalls of a retrospective study and as also being a study from a single institution, directly applying the results to daily clinical practice would be a premature approach. However, a prospective trial under this concept would not be ethical and impossible to be performed. Therefore, additional observational reports about the influence of treatment interval between completion of neoadjuvant chemotherapy and surgery on patient survival and pCR rate will be needed, to be comfortable with an 8-week interval.

Another essential aspect that must also be taken to account is the potential impact of treatment delay on patient anxiety. Although women know that it is necessary to wait for a treatment, it is experienced as a suffering time of anxiety and fear (16). Prolonged delay to surgical treatment will enhance this anxiety, and despite the results of this article, effort to minimize waiting time is one more thing a doctor could do for their patient.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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